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(54) Title: AN ANTIVIRAL PREPARATION AND THE METHOD OF ITS PRODUCTION

(57) Abstract

A biological preparation for the treatment of virus infections, and the procedure of its production. The principle of the method is to combine attenuated Gumboro virus with at least one registered carrier. The preparation which is the object of the invention is characterized by comprising attenuated Gumboro virus.

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AN ANTIVIRAL PREPARATION AND THE METHOD OF ITS PRODUC-TION

Object

The object of the invention is a biological preparaion for the treatment of virus infections. Object of the invention is also the procedure of its production, and further objects are the use of attenuated Gumboro virus or Gumboro virus vaccine for treatment of virus infections in humans, and the application of these preparations to humans.

The preparation is suitable for the treatment of practically any virus infection, and is particularly efficient against Herpesvirus infections, neoplastic diseases, aphthostomatosis and collagen diseases.

Professional information

Hepatitis virus infection damages the liver parenchyma. It has three different forms, known as epidemic hepatitis (hepatitis A virus infection), serum hepatitis (hepatitis B virus infection) and non-A-non-B (or C) hepatitis, a condition presumably caused by a hepatitis virus other than A or B.

The clinical course of the hepatitis A infection is relatively mild. Latency is usually 10-28 days. The patient is confined to bed for 30-45 days, and disability lasts still longer. The infection evokes specific immunity to further hepatitis A infection(s), but no vaccine is available for prevention.

Hepatitis B infection takes a more serious clinical course, and its latency is also longer, 50 - - 160 days. Virus B is much more resistant to thermic and chemical influences than virus A and most other viruses. Hepatocellular carcinoma is a frequent sequel to hepatitis B infection. This infection does not, as a rule, evoke an immune response. A vaccine prepared from the blood of convalescents is available against hepatitis B, but it has been little used on account of its possible side effects (AIDS) and high price.

As yet no preparation has been available for hepatitis therapy. The purpose of the present invention has therefore been to develop a biological preparation suitable for the therapy and control of viral hepatitis.

Disclosure of the invention

The object of the invention is the development, and method of production of an antiviral preparation containing attenuated Gumboro virus, with or without an adjuvant potentiating the latter's action. Object of the invention is also the application of the above preparations, and the use of attenuated Gumboro virus, in human therapy.

The Gumboro virus vaccine is known and widely used in the veterinary field.

The Gumboro disease is an acute viral disease of chickens, affecting them mainly at the age of 3-6 weeks. Its main symptoms are watery diarrhea, hyper-

trophy of the bursa of Fabricius, and inflammation of the lymphoid organs. In the USA the Gumboro disease, also known as infectious bursitis of chickens, was first described by Congreve in 1957. The disease also occurs in European countries, among others in Hungary. The causal agent of the disease, an enterovirus, is noted for its high resistance. The symptoms set in abruptly after a latency of 2-4 days, and usually subside after a week; most losses occur between days 3 and 5 of the clinical course. In the outbreaks studied, morbidity was 1-30 %, and mortality was 4-5 %.

The Gumboro vaccine, i.e. the attenuated Gumboro virus used by us is prepared by methods known from the literature. For example, a freeze-dried vaccine is prepared from attenuated virus propagated in primary or secondary fibroblast cultures from 10-11-day chick embryos. Sterile virus material of at least 10^6 $TCID_{50}$/0.1 ml titre may be used for production of the vaccine, as prescribed in the Pharm. Hung. VI. To the sterile virus material is added 50 % skim milk, and 2 ml amounts of the vaccine are distributed to 10 ml vials for freeze-drying.

The expiration time of the vaccine is one year when stored in sealed vials at +4 °C. Safety testing is performed in 15 SPF chickens aged 3 weeks; the birds must not show symptoms within 14 days of vaccination.

The freeze-dried vaccine is delivered in

packing units of 100, 200, 500 and 1000 doses, and is used for prevention of the Gumboro disease. It is administered orally, in the drinking water.

The vaccine described above is used as active substance of the preparation which is the object of the invention. Naturally the attenuated virus itself, or any solution (e.g. a physiological solution) thereof can also be used for that purpose.

The Gumboro virus is non-pathogenic for man even in its virulent state. Its attenuated form is doubly safe for humans.

Most human vaccines contain inactivated virus. However, the Gumboro vaccine - the object of the invention - is prepared exclusively from attenuated virus. The underlying mechanism of its antiviral action is presumably an interference phenomenon, more precisely a competition between the infecting virus and the vaccine virus.

We observed that the action of the attenuated Gumboro virus was potentiated mainly by certain tranquillizers. Of the latter the drugs of choice are the phenothiazine derivatives substituted usually in positions 2 and 10. Chlorpromazine (10-(3'-dimethyl-amino--propyl)-2-chloro-phenthiazine) proved to be the most effective compound in this respect. The range of the possible potentiating agents is, naturally, not limited to phenothiazine-like tranquillizers.

Apart from chlorpromazine, promethazine,

methophenazine, aminopromazine and similar compounds can be used as potentiating agents.

The attenuated virus component of the preparation which is the object of the invention should preferably be adsorbed onto a common carrier substance.

A freeze-dried vaccine with carrier proved to be the most advantageous, but the preparation can also be delivered in other forms, such as solution, suppository, capsule, emulsion, suspension, etc.

The applied dose depends on the patient treated, actual composition of the preparation, stage of disease and virus strain used. Of the attenuated virus 1000 to 5000 U, preferably 3000 - 4000 U, should be used daily either in a single dose or in 2-5 divided doses. Administration on 6 consecutive days is usually sufficient for full effect. Application may be oral or rectal, but where local therapy is required, as in Herpesvirus infections, the preparation can be applied in the form of solution or ointment.

With a potentiating agent added, the dosage also depends on patient, stage of infection and type of causative agent. For example, chlorpormazine may be administered at the daily dose level of 10-15 mg. A synergistic preparation should contain 10-100 mg chlorpromazine for each 1000 U of attenuated virus.

The preparations which are the object of the invention have been tested in many animal experiments and human trials, and developed in these a practically

100 % therapeutic effect against both hepatitis A and B, without any toxic side effect. They are suitable not only for symptomatic treatment, but also for prophylactic use: the contact persons of hepatitis A patients, given Gumboro virus preventively within 5 weeks of latency, did not contract the infection.

Further animal experiments and clinical trials in virus infections other than hepatitis have revealed the therapeutic efficiency of the preparations against many virus diseases.

The most promising results were obtained in the following conditions:

- Herpesvirus infections such as herpes simplex I, II, herpes zooster, cytomegalovirus disease, infectious mononucleosis (Epstein-Barr virus);
- various viral neoplastic diseases, above all liver cancer;
- aphthostomatosis;
- collagen diseases, e.g. polyarteritis nodosa.

Claims

1. Procedure for the production of a biological preparation against virus diseases, c h a r a c t e r i z e d by combination of attenuated Gumboro virus with at least one registered carrier.

2. Procedure according to claim 1, c h a r a c t e r i z e d by addition of a potentiating agent to the preparation.

3. Procedure according to claim 2, c h a r a c t e r i z e d by addition of chlorpromazine for potentiation.

4. Antiviral preparation c h a r a c t e r i z e d by comprising attenuated Gumboro virus.

5. Antiviral preparation according to Claim 4, c h a r a c t e r i z e d by comprising a registered carrier.

6. Preparation according to claim 4 and/or claim 5, c h a r a c t e r i z e d by comprising a potentiating agent.

7. Preparation according to claim 6, c h a r a c t e r i z e d by comprising chlorpromazine as potentiating agent.

8. Application of attenuated Gumboro virus or Gumboro virus vaccine for therapy of virus infections in humans.

9. Treatment of human virus infections with Gumboro vaccine or attenuated Gumboro virus.

10. Treatment of hepatitis with Gumboro

vaccine or attenuated Gumboro virus.

11. The treatment according to claims 9 and 10, c h a r a c t e r i z e d by using a potentiating agent.

INTERNATIONAL SEARCH REPORT

International Application No PCT/HU 85/00040

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[4].: A 61 K 39/12, A 61 K 39/39

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
Int.Cl[4]:	A 31 K 39/12, A 61 K 39/39

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X	DD, A, 143 793 (U. SCHMIDT, H. LIEBERMANN) September 10,1980 (10.09.80), see claims 1-3, page 1, lines 5-21; page 2, line 33 - page 3, line 23, example	(1,4,5)
X	AT, B, 308 967 (BEHRINGWERKE AKTIENGESELL-(SCHAFT) July 25, 1973 (25.07.73), see claim 1; page 2, lines 10-13, 43-49;	(1,4,5)
A	US, A, 3 548 055 (J.M. MOULTHROP) December 15, 1970 (15.12.70), see claims 1,4; column 1, line 65 - column 2, line 35	(1,4,5)
A	US, A, 3 885 011 (G. RENOUX, M. RENOUX) May 20, 1975 (20.05.75), see abstract; claims 7-9	(2,6)

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
19 September 1985 (19.09.85)	24 September 1985 (24.09.85)
International Searching Authority	**Signature of Authorized Officer**
AUSTRIAN PATENT OFFICE	Tschulena

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☒ Claim numbers 8-11 because they relate to subject matter not required to be searched by this Authority, namely:

Methods for treatment of the human or animal body by therapy - see Article 17(2)a)i) and Rule 39.1, iv).

2. ☐ Claim numbers....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim numbers..... because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Anhang zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.

Annex to the International Search Report on International Patent Application No. PCT/HU 85/00040

Annexe au rapport de recherche internationale relatif à la demande de brevet international n°.

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentdokumente angegeben. Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned International search report. The Austrian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

La présente annexe indique les membres de la famille de brevets relatifs aux documents de brevets cités dans le rapport de recherche internationale visé ci-dessus. Les renseignements fournis sont donnés à titre indicatif et n'engagent pas la responsabilité de l'Office autrichien des brevets.

Im Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
DD-A- 143 793	10/09/80	None	
AT-B- 308 967	25/07/73	BE-A1- 772 448	10/03/72
		CH-A - 560 760	15/04/75
		DE-A -2 045 160	30/03/72
		DE-B2-2 045 160	22/08/74
		DE-C3-2 045 160	10/04/75
		DK-B - 129 590	28/10/74
		DK-C - 129 590	24/03/75
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		FR-A5-2 106 482	05/05/72
		FR-B1-2 106 482	18/10/74
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		IL-A0- 37 682	29/11/71
		IL-A1- 37 682	30/06/74
		NL-A -7 112 237	14/03/72
		NL-B - 150 684	15/09/76
		US-A -3 769 400	30/10/73
US-A-3 548 055	15/12/70	None	
US-A-3 885 011	20/05/75	AU-A1-49 846/72	13/06/74
		BE-A2- 793 530	29/06/73
		CA-A1-1 007 567	29/03/77
		DE-A1-2 263 094	12/07/73
		FR-A1-2 230 345	20/12/74
		FR-B1-2 230 345	10/11/77
		IL-A0- 41 199	28/02/73
		NL-A -7 217 768	03/07/73
		ZA-A - 729 156	28/08/74